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10/034,950	12/26/2001	Bhami Shenoy	VPI/00-08	9344
1473 7590 02/26/2007 FISH & NEAVE IP GROUP ROPES & GRAY LLP 1211 AVENUE OF THE AMERICAS NEW YORK, NY 10036-8704			EXAMINER NOAKES, SUZANNE MARIE	
			ART UNIT 1656	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/034,950

Applicant(s)

SHENOY ET AL.

Examiner

Suzanne M. Noakes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 84-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 84-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

1. The amendments to the claims filed 15 November 2006 have been entered and are acknowledged. Claims 92-94 have been added which are commensurate in scope with the pending claims. Claims 84-94 are pending and subject to examination on the merits.

Withdrawal of Rejections/Objections

2. Any rejection not explicitly restated below is hereby withdrawn.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement:

4. The enablement rejection of claims 84 and 85 under 35 U.S.C., first paragraph, is maintained for the reasons of record and the reasons stated below. The details of the rejection can be found in the previous Office action in Section 8. New claim 94 is included in the instant rejection. Thus, claims 84, 85 and 94 are rejected.

5. The enablement rejection of claims 86-91 under 35 U.S.C., first paragraph, is maintained for the reasons of record and the reasons stated below. The details of the

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rejection can be found in the previous Office action in Section 9. New claims 92-94 are included in the instant rejection. Thus, claims 86-94 are rejected.

6. The enablement rejection of claims 90 and 91 under 35 U.S.C., first paragraph, is maintained for the reasons of record and the reasons stated below. The details of the rejection can be found in the previous Office action in Section 10.

Written Description:

7. The written description rejection of claims 84 and 85 under 35 U.S.C., first paragraph, is maintained for the reasons of record and the reasons stated below. The details of the rejection can be found in the previous Office action in Section 11. New claim 94 is included in the instant rejection. Thus, claims 84, 85 and 94 are rejected.

Response to Arguments

8. Applicant's arguments filed 15 November 2006 have been fully considered but they are not persuasive for the following reasons.

Enablement:

9. Applicants traverse the rejection of claims 84 and 85 as lacking enablement and that said claims are only enabled for the process of making Infliximab crystals as taught in Examples 34-37 and these arguments applicable to new claim 94.

It is Applicants position that the claims are enabled because for product claims the specification needs only one teaching of making the product. Furthermore, Examples 34-37 provide four different examples of making the product of Infliximab

crystals. Finally, other examples in the specification deal with making other whole antibody crystals, not just Infliximab, which provides support for claim 85.

However, this is not convincing. Specifically, while the disclosure of a single way of teaching a product does enable some products, in arts where the unpredictability is so great, more than one example may be required. Furthermore, in the case of protein crystallography, the art of making any crystal is so extreme that the disclosure of four ways to make said Infliximab crystal is not considered to be adequate because the scope of the claims allow for so many other species of Infliximab crystals (in claim 84), or *any* whole antibody crystal (claim 85), which encompasses vast number of potential crystals. As stated, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one or a few species, what other species will work. Likewise, it is not obvious from the disclosure if the same processes would work for Fab, Fab₂, or other variants of any Infliximab crystal and it is clear from the prior art that what works for one 'native' crystal may not work for another. Likewise the scope of claim 85 for *any* whole

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antibody crystal from any species or source, or any whole antibody variant (e.g. chimeric or humanized), encompasses so many different species whereas only a few examples exist in art of extreme unpredictability. Thus, the conclusion is that the claims exceed the scope of enabling disclosure.

10. Applicants traverse the rejection of claims 86-91 as lacking enablement and these arguments are similarly applicable to new claims 92 and 93. Specifically Applicants argue that the specification goes further than what the Examiner alleges, which is that the specification is only enabling for large batch crystallization of Retuximab and Trastuzumab, by teaching that the process described for these two antibodies are directly applicable to nine other specific antibodies listed in Example 38. Thus, this constitutes a specific teaching and as such the Examiner cannot only allege unpredictability because Applicants have successfully taught conversion from small microscale to large scale batch process which is applicable to every antibody.

The Examiner disagrees with this assessment, however. There is no dispute that Applicants have taught how to crystallize two antibodies in a large scale batch method based upon the micro-batch conditions. However, the leap between asserting that this therefore teaches how to successfully produce antibody crystals for all antibodies in the same manner is more than the prior art teaches is reasonable to expect. Applicants suggest that the Examiner cannot rely only on the unpredictability factor. However, in protein crystallization methods, there is clearly no escaping this factor. Furthermore, unpredictability is not the only factor outlined by the Examiner, it is one of eight factors (Wands factors) that culminate in the conclusion that the claims are not enabled for the

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entire scope. As was outlined in the previous Office action, the Wands factors of (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims all were taken into consideration. The conclusion is and was that the quantity of experimentation necessary to practice the entire scope of the claimed subject matter is enormous (1) because finding successful micro-batch crystallization conditions in the first place is extremely difficult and unpredictable in the science which is then further complicated and compounded by the fact that it is not exactly straight forward to leap from microbatch conditions to large scale production; (2 and 3) the amount of direction in the specification provides for two examples which may or may not work for other antibodies, (4) the nature of the invention is that crystallization of anything at all is extremely difficult and difficult, (5-8) the nature of the prior art suggests crystallizing anything is nothing but trial-and-error, even today with all of the advances in technology and automated robotic assistance, there is nothing predictable or easy about crystallizations. In fact, it is very well known in the art that luck often times is one of the main factors in facilitating successful crystallizations. Cudney et al. (see "Protein Crystallization and Dumb Luck", entire article, The Rigaku Journal. 1999. Vol. 16, No. 1, pp. 1-7.) describe the role of luck in many different crystallization experiments in his own lab and acknowledge that nearly every single crystallographer in existence has similar stories of fortuitous crystal growth and that they do not, however, publish these

"findings" for fear of looking foolish. Furthermore, large scale production of therapeutic proteins are very well known, insulin (see US 4,959,351 and 6,310,038) and human growth hormone (see US 5,780,599) are just two of the many therapeutic protein crystals which have been scaled up for production of large scaled production using very similar methods that Applicants are claiming. However, what makes the instant invention and others like it non-obvious is the crystallization of specific proteins or antibodies that have been successfully produced and is non-obvious because of the fact that what does work for one protein or antibody will not necessarily work for another, even if you have starting conditions to begin with. Furthermore, in claims 86, 92 and 93, what guidance in the specification is there for "preparing a series of different micro-batch crystallization solutions each of a total volume of at least 33/75/100 μ l wherein each solution comprises the antibody and different crystallization buffer" other than the specific examples for specific antibodies. The crystallization buffer works for each different antibody will be different and a grand assertion that the conditions taught by Applicants will work for all antibodies on a microscale goes against the teachings of the prior art. For instance, even if you had the conditions to successfully produce whole antibody crystals, the same conditions are likely completely different for any derivative thereof, e.g. Fab, Fab₂, single chain Fv, etc. because the prior art teaches for example, that there 25 different parameters which do or could affect crystallization of each protein/antibody (see McPherson (Eur. J. Biochem. 1990, 189:1-23), Table 2, p. 13) and that each protein is assessed on its own biophysical characteristics. It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

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"Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins."

Furthermore, even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. Cell. Mol. Life Sci. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein or antibody that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

For these reasons, the breadth of the claims exceed that which is enabled by the specification. And for these reasons lack of enablement is considered proper.

11. Applicants traverse the rejection of claims 90 and 91 as lacking enablement and that said claims are only enabled for the process of making Infliximab crystals as taught in Examples 34-37 and these arguments are applicable to new claim 94.

Applicants assert that the specification teaches how to make Infliximab crystals from four different microbatch crystallization conditions. Thus, if one follows the

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teachings of the specification, one should be able to produce crystals of Infliximab from the outlined large scale process. It is also asserted that Applicants have in fact produced large batches of Infliximab crystals using the diverse methods. And that the Examiner has proved no reason why these buffers would not produce Infliximab crystals in a large batch crystallization.

However, the Examiner disagrees. In the first instance, the Examiner can find no disclosure in the specification where Infliximab crystals have been produced by the large batch methods as stated in the response. Every example of crystallization of Infliximab was performed on the microscale level and not translated or scaled-up to the large scale method. Furthermore, the assertion that the Examiner has provided no reason why these buffers would not produce Infliximab crystals is erroneous. The prior art points to the fact suggests otherwise and is what was stated in the previous Office action. Jen et al. (Pharm. Res. 2001, 18(11):1483-148), teach an overview of the success over the years of producing protein crystals on a large scale for the use in pharmaceuticals, specifically state the following (p.1487, 1st column, 2nd paragraph):

“Once a crystal candidate has shown promising properties for pharmaceutical development, the crystallization effort must be up-scaled. The batch and dialysis methods are likely the easiest options for adaptation to large-scale crystallization because similar constructions already exist for chemical, pharmaceutical, and biotechnological processes. The conversion of microliter-size crystallization trials into industrial dimensions, however, may be a challenging task.”

Applicants seem to completely dismiss what the prior art teaches and that the predictability in going from the small to large scale is not a trivial matter which will work consistently for every single antibody and that each antibody needs be taken on a case by case basis.

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As further evidence of the problems of scaling from small scale to large is given by Klyushnichenko (Curr. Op. Drug Discovery, 2003, 6(6):848-54) wherein the following is taught (p. 849, 1st column, 2nd paragraph):

The objectives of a bulk protein crystallized process are to rapidly purify and concentrate the produce with high yield and without loss in potency. However, crystallization has not been used widely in the purification or formulation of biological compounds. This is due to the difficulties in developing crystallization conditions that are reproducible and scalable at clinical- and commercial-scale.

Klyushnichenko does give several examples where successful conversion from microscale to large scale crystallization has been achieved, most notably in insulin formulations. However it is also taught:

As discussed above, there are several examples of large-scale protein crystallization; however, researchers frequently report that no clear understanding of the protein crystallization mechanism has yet emerged. Typically several hundred experiments must be performed to determine crystallization conditions, such as pH, buffer type, precipitant type and protein concentration. To control costs and improve efficiency, it is important to minimize the number of experiments, especially if the final or intermediate conditions are to be scaled-up.

The enablement requirement clearly delineates the predictability in the art and correlates this with the amount information necessary in the specification. If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification needs more detail as to how to make and use the invention in order to be enabling. In the instant case, however, the nature of the invention and the prior art readily acknowledges the challenges and unpredictability in the art. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily

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anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

"[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]"

In the instant case, what is known in the art and the required undue experimentation imposed upon one skilled in the art because the breadth of the claims exceed that which is sufficiently supported in the specification is supportive of the lack of enablement for said claims.

Written Description:

12. Applicants traverse the rejection of claims 84 and 85 as not having written description for said claims and not being in possession of all Infliximab crystal, or whole antibody crystals. These arguments applicable to new claim 94.

Applicants assert that because they have described how to select appropriate crystallization buffers and shown several successful working examples, that they are in

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possession of the entire genus of all Infliximab crystals or whole antibody crystals. It is further asserted that the Examiner has relied upon art that is essentially not relevant to the instant scenario because the instant Application describes large batch crystallization methods and techniques and not those crystallization techniques which are used for X-ray structural analysis wherein the crystal quality needs to be very high. It is also asserted that the common feature is that of antibody crystals which has been described and a skilled artisan need only to simply select the appropriate buffer to use in microcrystallization and use the selected buffer in a large batch crystallization.

However, this is unconvincing because "simply selecting" the appropriate buffer is difficult enough. Which one will work for all antibody crystals? It clearly is a diverse combination as demonstrated by all of Applicants examples, and it is not just one buffer which will work. It is a mixture of salt, pH, temperature, solvents, additives, buffer choice, protein concentration, etc.. So which one, or which combinations do Applicants suggest will work for all antibody crystals? The art clearly suggests that it is not just one and McPherson et al. suggest it is a combination of 25 different parameters, not simply one. Furthermore, the scope of the Applicants claims (84 and 94) does encompass every single Infliximab crystal derivative, homolog or variant thereof, every Fab, Fab₂, single chain antibody, etc., for batch crystallization *and* structural determination. Likewise, claim 85 for the whole antibody crystals of every single potential and conceivable kind of antibody, from any source, derivatized in any manner (e.g. chimeric, humanized, etc.) which is 20 mg/ml or more in concentration. In order for a broad generic claim to have written description, the specification must provide

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adequate description in the specification to identify the genus of the claim by describing a sufficient number of representative species. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Thus, the species which are described in the specification are not deemed to be representative of the entire genus of antibody crystals for which the claims are drawn to.

13. Applicant's arguments with respect to claim 85 have been considered but are moot in view of the new ground of rejection which was necessitated by amendment.

New Rejections – Necessitated by Amendments

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 85 is rejected under 35 U.S.C. 102(b) as being anticipated by Ely et al. (Biochemistry, 1978, 17(5):820-23).

The claim is drawn to an pharmaceutical composition comprising a whole antibody wherein the concentration of said antibody is greater than 20 mg/ml.

Ely et al. teach the crystallization of the whole antibody of human IgG2 wherein the antibody is at a concentration of 20-22 mg/ml and the process of crystallization is by microdiffusion against 0.1M borate, 0.05M NaCl at pH 7.0 (see p. 820, 2nd column, last line to p. 821, 1st column, first line). Thus the crystal forms in a pharmaceutically acceptable buffer and is thus in a pharmaceutical composition.

Conclusion

16. No claim is allowed.
17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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